The occurrence of radiation-induced toxicity is a very complex process that is always modulated by the individual [2]; if two patients receive the "same dose distribution" they will likely have different reactions and possibly one will experience toxicity while the other not. The availability of individual information potentially characterizing the patient response, including the "omics" information, is highly valuable, especially in the "high-tech" era of image-guided/adaptive IMRT in which organs are more efficiently spared: the better sparing reduces the incidence and severity of toxicities and, at the same time, enhances the impact of individual sensitivity factors. This point reinforces the need to create large data bases including individually assessed clinical, biological and genetic information, in addition to the individual dose distribution. As a consequence, the approach of quantitatively modelling dose-volume relationships is increasingly becoming "phenomenological" [3]: robust methods for (dosimetric and non-dosimetric) variable selection able to condense the information in "reliable", friendly to use, predictive models is a major field of research: the adaptation of statistical methods for data-mining and to avoid over-fitting is a pivotal point of the story.

Although the potentials of large data bases and of data sharing platforms on toxicity modelling are clear [4], we should not forget that the creation of large data-bases is not the "aim" but is a (powerful) "tool". The outcome of the process in terms of robustness and reliability of the models will not only depend on the "numbers" (a highly important component) but also (and maybe more importantly) on the "quality" of data. Differently from the "easy" score of the success of a therapy (survival, tumour control), toxicity is a much more complex issue that deserves specific attention and the careful collection of patient-reported and/or physician-reported information, often for years. Well assessed prospective observational studies focused on specific toxicities seem to be the best choice; secondary analyses of high-quality data coming from controlled trials are also very important although they may be limited in some cases by too homogenous protocols restricting the spread of the delivered dose distributions.

At the end of the circle, the external validation of integrated dose-volume models is clearly a crucial component of the next year's research [3]: testing the generalizability of dose-volume models will be a major end-points. In addition, robust results from phenomenological models are expected to feed up mechanistic approaches in a sort of mutual synergy that can further corroborate our knowledge: these two components (mechanistic and phenomenological) will likely cooperate much more in the next future. Relevant developments are expected to impact the quantitative modelling of normal tissue effects also from the side of the dosimetry data. The robust, organ-planning-DVH approach to quantitatively describe the relationship between dose/volume and toxicities should be overcome/refined in many relevant situations by directly looking to the 3D dose distribution, integrating the spatial information lost when using "classical" surrogates like DVH/EUD. Relevant examples are: the direct measurement of dose-map dissimilarities between patients [5], the quantification of local (and organ) effects by imaging biomarkers [6], the interplay between the dose received by different organs, the impact of anatomy changes during therapy and their incorporation into normal tissue predictive models.

Quantitative modelling of normal tissue effects is lively present in current century and seems to have a brilliant future in contributing to rapidly improve the way we treat our patients with the promise to continuously reduce toxicity.

1-Marks LB et al. Int J Radiat Oncol Biol Phy. 2010;76 (Suppl 1):S10-S19.
2-Bentzen SM. Nature Rev Cancer. 2006;6:702-713
3-van der Schaaf A et al. Int J Radiat Oncol Biol Phys 2015;91:468-471
4-Deasy JO et al. Int J Radiat Oncol Biol Phys 2010; 76 (Suppl 1):S151-S154
5-Acosta O et al. Phys Med Biol 2013;58:2581-95
6-Fiorino C et al. Radiother Oncol 2012;104:224-229.

Teaching Lecture: Shared decision making

SP-0384
Shared decision making

D. Tomson[1]
[1]*Institute of Health and Society Newcastle University, Newcastle Upon Tyne, United Kingdom*

Drawing on experience as a practicing GP with a special interest in communication skills and shared decision making, the work of The Health Foundation funded MAGIC (Making Good decisions in Collaboration) programme and most recently on a collaboration with a Danish Oncology Hospital, Dr Dave Tomson will explore recent developments in Shared Decision Making (SDM). Using experience and expertise from the delegates we will

a) check out attitudes and beliefs about the need and rationale for putting SDM centre stage in patient interactions,
b) look at a useful model of SDM both for personal clinical practice and for teaching other clinicians,
c) explore some of the key skills needed and the key challenges in doing better SDM with a particular focus on oncology – the constant changing nature of the evidence base, individualised care in a guideline driven world, dealing with personal bias, unwarranted versus warranted variation in practice, the tyranny of time.
d) share some ideas about possible solutions to these challenges and think about some of the steps needed to both develop personal practice and implement programmes of development within departments and across hospital systems

Teaching Lecture: The study of therapy resistance in genetically engineered mouse models for BRCA1-mutated breast cancer

SP-0385
The study of therapy resistance in genetically engineered mouse models for BRCA1-mutated breast cancer

S. Rottenberg[1], M. Barazas[2], J. Jonkers[2], G. Borst[3]
[1]*University of Bern, Institute of Animal Pathology, Bern, Switzerland*
[2]*The Netherlands Cancer Institute, Molecular Pathology, Amsterdam, The Netherlands*
[3]*The Netherlands Cancer Institute, Division of Radiotherapy, Amsterdam, The Netherlands*

Although various effective anti-cancer treatments have become available over the last decades, therapy resistance remains the major cause of death of cancer patients. Striking examples are patients with tumors that are defective in DNA repair by homologous recombination (HR). Despite initial responses to cancer therapy, resistance of primary or disseminated tumors eventually emerges, which minimizes therapeutic options and greatly reduces survival. The molecular mechanisms underlying this therapy escape are often poorly understood.

A clinically relevant mechanism for the defect in HR is a lack of function of BRCA1. This defect impairs error-free repair of DNA double-strand breaks (DSB) – a feature that can be exploited by the treatment with DSB-inducing agents. Using the *K14cre,Brca1F/F,p53F/F* (KB1P) genetically engineered mouse model for BRCA1-mutated breast cancer, we have shown the success of this strategy. Tumors are highly sensitive to DNA cross-linking agents, or to the inhibition of topoisomerase I/II and poly (ADP-ribose) polymerase (PARP) (reviewed by Rottenberg & Borst, 2012). Despite this sensitivity, tumors are not eradicated and eventually drug-refractory tumors emerge. In several of the resistant tumors we found that the HR defect can be partially rescued by down-regulation or knock-out of additional repair factors, such as 53BP1 (Jaspers *et al.* 2013) or REV7 (Xu *et al.* 2015).

Based on these observations we set out to investigate whether this type of HR restoration can also explain radiotherapy resistance. For this purpose, we treated mice carrying KB1P tumors with high-precision radiotherapy. We

observed that KB1P tumors were initially hypersensitive to fractionated local delivery of radiotherapy, but could not be eradicated: tumors relapsed and eventually acquired stable resistance. To investigate whether HR was restored in the resistant tumors, we studied 53BP1 and RAD51 irradiation-induced foci formation. Surprisingly, while restoration of HR was prominently found in tumors that acquired resistance to PARP or topoisomerase I inhibition, we did not find it in radiotherapy resistant tumors. To investigate this discrepancy more closely, 53BP1 and related repair factors were knocked out in cell lines derived from the KB1P model using the CRISPR/Cas9 technology. Consistent with our *in vivo* data, clonogenic assays showed that the knock-out of 53BP1 conferred strong resistance to PARP1 inhibition. Intriguingly, the lack of 53BP1 sensitized BRCA1-deficient cells to radiotherapy. An *in vitro* competition assay confirmed the selection to maintain a functional 53BP1 allele during radiotherapy treatment. Based on the KB1P model, we therefore hypothesize that resistance mechanisms that frequently occur in response to PARP1 inhibition sensitize cells to radiotherapy. These results, and their significance to human cells, are currently further validated in additional *in vivo* models including patient-derived tumors.

References
- Jaspers *et al.* (2013). Loss of 53BP1 causes PARP inhibitor resistance in Brca1-mutated mouse mammary tumors. 3:68-81.
- Rottenberg & Borst (2012). Drug resistance in the mouse cancer clinic. *Drug Resistance Updates* 15:81-9.
- Xu *et al.* (2015). REV7 counteracts DNA double-strand break resection and affects PARP inhibition. *Nature* 521:541-4.

Teaching Lecture: SBRT/SABR for oligometastatic disease

SP-0386
SBRT/SABR for oligometastatic disease

E. Lartigau[1]
[1]*Centre Oscar Lambret, Lille, France*

Introduction: Stereotactic (ablative) body radiotherapy (SBRT/SABR) has been successfully used in the treatment of metastatic lesions and could be considered as a "curative option" for some oligometastatic patients. Multiple studies have described significant local control in brain, lung and liver metastases of various primary cancers. Results suggest SBRT/SABR could be an effective treatment extending patients' life span.

Study: For example in our retrospective study involved 90 patients, designed to test potential effectiveness of SBRT in the treatment of oligometastases irrespective of primary Between July 2007 and June 2010, 90 patients were treated with robotic SBRT/SABR for hepatic or pulmonary metastatic lesions. A total of 113 liver and 26 lung metastatic lesions in 52 men (58%) and 38 women (42%) were treated. Median follow-up was 17 months. Median age at treatment was 65 years (range, 23-84 years). Primary cancers were 63 GI, three lung, eight breast, four melanoma, three neuro-endocrine tumors, and three sarcomas. Median diameter of the lesions was 28 mm (range, 7-110 mm) for liver and 12.5 mm (range, 5-63.5 mm) for lung. Local control rates at 1 and 2 years were 84.5% and 66.1%, respectively. Two-year overall survival rate was 70% (95% CI: 55-81%). The 1 and 2-year disease-free survival rates were 27% (95% CI: 18-37%) and 10% (95% CI: 4-20%), respectively. Median duration of disease-free survival was 6.7 months (95% CI: 5.1-9.5 months). Observed toxicities included grade 1-3 acute toxicities. One grade 3 and no grade 4 toxicity were reported. High-dose SBRT/SABR for metastatic lesions is both feasible and effective with high local control rates.

Discussion: In the last 4 years, some reports have described the so call abscopal effect described as "*an action at a distance from the irradiated volume but within the same organism.*" Abscopal effect may be more pronounced in response to ablative (> 10 Gy) rather than conventional dosage or fractionation schedules and has been reported mostly in renal cell carcinoma and in melanoma. The effect is attributed to activation of the systemic immune response by increase antigen presentation (neo antigens released after rapid cell necrosis) and enhanced immune response. These concepts may be of clinical value, improving outcomes by inducing systemic abscopal effects and potentially combined SBRT/SABR with immunotherapy or lymphocytes activating agents. Furthermore, these results have raised the question whether classic radiobiological modeling, and the linear-quadratic (LQ) model, are appropriate for large doses per fraction with the possibility of such an additional biological effects resulting from endothelial cell damage, enhanced tumor immunity, or both. These concepts will be discussed at the time of presentation.

Conclusion: SBRT/SABR treatment is well tolerated with low toxicity rates. It could represent an interesting treatment option for oligometastatic patients not amenable to surgery, even when patients had been pre-treated with chemotherapy. The biological models behind the observed clinical efficacy are currently scrutinized. New combined treatment may be driven from such promising results.

Teaching Lecture: Advanced treatment strategies for head and neck cancer

SP-0387
Advanced treatment strategies for head and neck cancer

W. Budach[1]
[1]*University Hospital Düsseldorf Heinrich Heine University Düsseldorf, Düsseldorf, Germany*

Optimal treatment of head and heck squamous cell carcinoma (HNSCC) patients requires well organized interdisciplinary coordination. Standard treatment of locally advanced HNSCC is chemoradiation or surgery followed by chemoradiation. Cisplatin containing chemotherapy remains standard of care in combination with concurrent radiotherapy. Neither neoadjuvant chemotherapy, nor treatments with targeted drugs have changed this standard, although some data suggest that cetuximab can be used as substitute for cisplatin especially in HPV/p16 positive disease. Combinations of cetuximab or other EGFR1 antagonists with chemoradiation did not improve patient's outcome, but added toxicity. Overall, attempts to improve clinical outcome in locally advanced HNSCC with targeted drugs and new cytostatic drugs have not been successful. The situation is different in locoregionally recurrent HNSCC not amenable for local treatment and in metastatic disease. In these patients, the addition of cetuximab to cisplatin and 5FU resulted in a significant survival benefit and consequently is considered as standard of care.

HPV/p16 positive HNSCC represents a distinct entity, which is more sensitive to radiotherapy and cytotoxic drugs. Several strategies testing deescalated treatments are being tested in randomized trials. However, deescalated is not yet recommended outside clinical trials.

Neoadjuvant chemotherapy followed by radiotherapy +/- chemotherapy or cetuximab, and primary chemoradiation have been shown to allow for organ preservation especially in laryngeal cancer in the majority of patients without compromising overall survival. However, adequate selection of patients is critical to obtain organ preservation with good functional outcome.

Recent technological developments in surgery and radiotherapy like transoral robotic surgery and radiotherapy using intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), image guided radiotherapy (IGRT), and stereotactic body radiation therapy (SBRT) have been evaluated in cohort studies and a few randomized trials. These technologies are suitable for decreasing early and late toxicity and improvement of functional outcome, but have not been shown to improve locoregional control, disease free survival, and overall survival.

The available data on the topics addressed above will be shown and discussed.